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REC'D 10 DEC 2004
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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REP07284WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03720	International filing date *(day/month/year)* 28.08.2003	Priority date *(day/month/year)* 29.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/519		
Applicant ARACHNOVA THERAPEUTICS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.02.2004	09.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Borst, M Telephone No. +49 89 2399-8648

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03720

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-5 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV

Lack of unity of invention

1. The present European application has been found to include the following (groups of) inventions:
   Use of MCI 225 or a salt thereof for the manufacture of a medicament
   I for the treatment of fibromyalgia (claim 1), premenstrual syndrome (claim 5), migraine (claim 7), fatigue (claim 14)
   II for the treatment of obesity/weight gain (claim 2), eating disorders (claim 6), nausea/vomiting (claim 10), chemotherapy/radiation induces emesis (claim 11)
   III for the treatment of substance abuse/drug addiction (claim 3), smoking cessation (claim 4)
   IV for the treatment of Parkinson's disease (claim 8), stroke (claim 9), schizophrenia (claim 12), obsessive compulsive disorders (claim 13)

2. The present claims are directed to further uses of MCI 225 in therapy.
   According to the description (page 1, line 1-4) the problem to be solved with the subject-matter of the claims on file is to provide new therapeutic uses for MCI 225.
   Thus, the single concept linking the subject-matter of the individual claims to gether is the use of MCI 225 in therapy.
   However, this concept is already known from EP 0 150 469 (table 1-3; page 19), Eguchi Junichi et al. "Effects of MCI-225 on Memory and glucose utilization in basal forebrain-lesioned rats", Pharmacology Biochemistry and Behavior, 1995, vol. 51, nr. 4, pages 935-939 (page 938-939, paragraph entitled "Discussion"), or XP002239887 (page 681-682, paragraph entitled "4. Discussion") disclosing MCI 225 for use in depression or cognitive disorders.
   Since there is no other concept, that could fulfil the role of single inventive concept in the sense of Rule 13(1) PCT, the present application lacks unity of invention *a posteriori*, containing the subjects as listed under item 1 above.

3. For the time being the claims on file, although not meeting the requirements of unity, could be examined without effort justifying an additional fee.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: EP-A-0 150 469 (MITSUBISHI CHEM IND) 7 August 1985 (1985-08-07)
D2: EGUCHI JUNICHI ET AL: "Effects of MCI-225 on Memory and glucose utilization in basal forebrain-lesioned rats" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, vol. 51, no. 4, 1995, pages 935-939, XP002257547 ISSN: 0091-3057
D3: EGUCHI J ET AL: "The anxiolytic-like effect of MCI-225, a selective NA reuptake inhibitor with 5-HT3 receptor antagonism" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, ELSEVIER, US, vol. 68, no. 4, April 2001 (2001-04), pages 677-683, XP002239887 ISSN: 0091-3057
D4: RAO S G: "THE NEUROPHARMACOLOGY OF CENTRALLY-ACTING ANALGESIC MEDICATIONS IN FIBROMYALGIA" RHEUMATIC DISEASES CLINICS OF NORTH AMERICA, W.B. SAUNDERS, PHILADELPHIA, PA, US, vol. 28, no. 2, 2002, pages 235-259, XP009005801 ISSN: 0889-857X
D5: WO 00/15223 A (IYENGAR SMRITI ;LILLY CO ELI (US); GOLDSTEIN DAVID JOEL (US); SIMM) 23 March 2000 (2000-03-23)
D6: WO 02/060427 A (SEPRACOR INC) 8 August 2002 (2002-08-08)
D7: WO 02/064543 A (WYETH) 22 August 2002 (2002-08-22)
D8: HEAL D J ET AL: "SIBUTRAMINE: A NOVEL ANTI-OBESTIY DRUG. A REVIEW OF THE PHARMACOLOGICAL EVIDENCE TO DIFFERENTIATE IT FROM D-AMPHETAMINE AND D-FENFLURAMINE" INTERNATIONAL JOURNAL OF OBESITY, NEWMAN PUBLISHING, LONDON, GB, vol. 22, no. SUPPL 1, August 1998 (1998-08), pages S18-S28, XP008005119 ISSN: 0307-0565
D9: WO 96/12485 A (LILLY CO ELI) 2 May 1996 (1996-05-02)
D10: WO 2004/062624 29 July 2004 (cited by the Applicant)

1. Novelty (Article 33(2) PCT)

The subject-matter of the independent claims on file appears to be new.
D1-D3 do not disclose the therapeutic indications defined in the independent claims on file.
D4-D9 do not disclose MCI 225.

2. Inventive step (Article 33(3) PCT)

2.1. The subject-matter of claims 1-15 on file does not involve an inventive step in the light of D4-D9 combined with D1-D3.
With the submission dated 01.10.2004 the Applicant points out that MCI-225 is not a pure SNRI, but shows further activities, such as inhibition of 5HT3 receptors, and that the mechanisms underlying its action are still incompletely understood. This

argument could be considered as a positive pointer for inventive step insofar as it establishes a mechanism of action for MCI-225 different from that of other SNRI's, such as duloxetine, sibutramine, venlafaxine. However, this argument can be taken into account only if it is supported by appropriate evidence. At present only a reference to the Drug Report on MCI-225 from the Investigational Drug Database is on file. In the absence of said document itself, the previously raised objection under Article 33(3) PCT is to be maintained.

It is known from D4 (page 246, last full paragraph), D5 (page 1, line 17-19; claim 4), D6 (page 1, line 7-20; page 7, line 16-26; page 11, line 10-13; page 14, line 11-17), D7 (page 11-17; claim 43, 47), D8 (page S26-S27, paragraph entitled "Summary"), D9 (page 1, line 17-20, claim 1-3) that serotonine noradrenaline reuptake inhibitors (SNRI's), such as duloxetine, sibutramine, venlafaxine, are effective in the treatment of the pathological conditions defined in claims 1-14 on file.

The objective technical problem to be solved in the light of D4-D9 was, therefore, to provide further compounds which are suitable for treating said conditions.

D1 (table 1-3; page 19), D2 (page 938-939, paragraph entitled "Discussion"), D3 (page 681-682, paragraph entitled "4. Discussion") disclose that MCI 225 belongs to the class of SNRI's. Therefore, it was obvious in the light of D4-D9 combined with D1-D3 to use MCI 225 for the treatment of the pathological conditions defined in claims 1-14 on file, in particular as the application on file does not provide any experimental evidence substantiating the effectiveness of MCI 225 in the treatment of the diseases claimed.

2.2. Additionally, the subject-matter of claims 1-10,12-15 on file does not involve an inventive step, because the problem of treating the diseases claimed is not solved.

In the submission dated 01.10.2004 the Applicant refers to various clinical studies on the use of MCI-225 for the treatment of depression and Alzheimer which have been discontinued and concludes that the doubt about the efficacy of MCI-225 for the above indications "must equally apply to <u>any</u> therapeutic utility of the compound".

The present application now claims the use of MCI-225 for the treatment of a huge number of diseases without providing any experimental evidence substantiating the therapeutic effectiveness of MCI 225. As already the Applicant has doubts as to <u>any</u> therapeutic utility of the compound, there is good reason also for the International examining auhority to draw into question the therapeutic effectiveness of MCI-225 in the treatment of the diseases defined in the claims. Therefore, in the absence of any technical evidence to the contrary, which is provided neither with the application nor

with any further submission of the Applicant, the problem of treating the diseases claimed is to be considered as not solved. The technical problem not being solved inventive step cannot be acknowledged.

2.3. The subject-matter of claim 12 on file does not involve an inventive step in the light of the known mechanism of chemo-/radiotherapy induced emesis and of the receptor activity of MCI-225.

The only therapeutic indication for which experimental evidence (D10) has been submitted is chemotherapy-induced emesis. Here, the Applicant states that cisplatin like radiotherapy "is known to produce emesis through the stimulation of 5HT3 receptors". As confirmed in the Applicant's submission MCI-225 was known to be a 5HT3 receptor antagonist (cf. item 2.1. above). Therefore, in view of the known mechanism of chemo-/radiotherapy induced emesis and of the receptor activity of MCI-225 it was obvious to use MCI-225 for this therapeutic indication.